is attached hereto as **Exhibit A.**

REMARKS

Claims 1-24 were pending in the subject application. By this Amendment, applicant has amended claims 1, 2, 7, 8, 13, 14, 19 and 20; and added new claims 25-26. Accordingly, upon entry of this Amendment, claims 1-26, will be pending and under examination.

Applicant maintains that the amendments to claims 1, 2, 7, 8, 13, 14, 19 and 20 do not raise any issue of new matter and that these amendments are fully supported by the specification as originally-filed on page 14, lines 36-37; and page 8, line 36 through page 9, line 1.

Support for new claim 25 may be found inter alia in the specification as originally-filed on page 9, lines 22-26; and page 8, line 36 through page 9, line 1. Support for new claim 26 may be found inter alia in the specification as originally-filed on page 25, Table 1.

Accordingly, applicant respectfully requests that the Amendment be entered.

Rejection Under 35 U.S.C. § 112, first paragraph

On page 2 of the November 18, 2002 Office Action, the Examiner rejected claims 1-24 under 35 U.S.C. 112, first paragraph, because the specification while being enabling for treating human urinary incontinence with compound 1 or compound 2 which can activate the human 5-HT_{1F} receptor, allegedly does not reasonably provide enablement for treating human urinary incontinence with

any kind of 5-HT_{1F} receptor agonist at least 10 fold more than it activates one of the receptors as recited in claims 1-24. The Examiner further alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner stated that the Court summarized eight factors to be considered in a determination of "undue experimentation." (See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).) The factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The Examiner then alleged that there is no direction or guidance in the specification to show that: (1) any kind of 5-HT_{1F} receptor agonist which can activate the human 5-HT_{1F} receptor at least 10 fold more than it activates one of the receptors as recited in claims 1-24 can treat human urinary incontinence; and (2) any kind of 5-HT_{1F} receptor agonist can bind to the receptors as recited in claims 1-24.

The Examiner acknowledged that human urinary incontinence can be treated with compound 1 and compound 2 of the instant specification and that 5-HT_{1F} agonists are well-known in the art. The Examiner alleged that it is unclear whether any kind of 5-HT_{1F} receptor agonist which can activate the human 5-HT_{1F} receptor at least 10 fold more than it activates one of the receptors as recited in claims 1-24 can be used to treat human urinary incontinence. The Examiner also alleged that it is unclear

whether any kind of 5-HT_{1F} receptor agonist can bind to the receptors as recited in claims 1-24.

The Examiner alleged that there will be a lot of unpredictable factors when the skilled artisan uses the claimed method to treat human urinary incontinence and that the skilled artisan will have no way to predict the experimental results. The Examiner concluded that such efforts constitute undue experimentation. The Examiner alleged that the undue experimentation at least includes the need to test: (1) whether any kind of 5-HT_{1F} receptor agonist which can activate the human 5-HT_{1F} receptor at least 10 fold more than it activates one of the receptors as recited in claims 1-24 can be used treat human urinary incontinence; and (2) whether any kind of 5-HT_{1F} receptor agonist can bind to the receptors as recited in claims 1-24.

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicant has amended claim 1 and claims 2, 7, 8, 13, 14, 19 and 20. Applicant points out that claims 2-24 and new claims 25-26 depend on claim 1.

New claim 1 recites:

> A method of treating urinary incontinence in a human subject suffering from urinary incontinence which comprises administering to the human subject a therapeutically effective amount of a 5-HT_{1F} receptor agonist which selectively activates the human 5-HT_{1F} receptor.

Applicant believes that the Examiner has misunderstood the subject invention. Applicant maintains that the invention as reflected in amended claim 1 is the discovery that selective human 5-HT_{1F} receptor agonists can be used to treat urinary incontinence. With respect to claim 1, as amended, applicant

points out that the binding characteristics of the 5-HT_{1F} receptor agonist at other receptors is no longer recited.

Applicant maintains that the art of GPCR technology teaches that GPCRs may be coupled to a specific biological effect. The subject invention relates to the discovery of a role for the GPCR named 5-HT_{1F} receptor in the micturition reflex (see page 4, lines 19-28 of the specification). Applicant maintains that provided with the teachings of the specification, one skilled in the art of GPCR technology would recognize that it is reasonably predictable with a reasonable likelihood of success that 5-HT_{1F}-selective compounds which activate the human 5-HT_{1F} receptor can be used in the treatment of urinary incontinence.

Applicant points out that the Examiner has acknowledged that 5-HT_{1F} receptor agonists are well known in the art (see page 4 of the November 18, 2002 Office Action). The Examiner has also acknowledged that the claims are enabled for treating human urinary incontinence with compound 1 and compound 2 (see page 2 and page 4 of the November 18, 2002 Office Action). Applicant maintains that compound 1 and compound 2 are working examples of selective human 5-HT_{1F} receptor agonists. Applicant maintains no undue experimentation is required to determine the <u>selectivity</u> of such well-known 5-HT_{1F} receptor agonists and to subsequently practice the method as recited in claim 1 using selective agonists.

Applicant maintains that 5-HT_{1F} receptor agonists are routinely tested in binding assays by the skilled artisan so as to determine selectivity. Applicant notes that determinations of selectivity is recognized as being useful in the relevant art as this permits the artisan to predict the side effect profile of compounds. Applicant maintains that it is not undue

experimentation, but rather, a matter of routine experimentation for the skilled artisan to test the binding of compounds to receptors to define selective human 5-HT_{1F} receptor agonists.

Applicant points to *In re Wands,* 858 F.2d 731, 736 (Fed. Cir. 1988):

> "Enablement is not precluded by the necessity for some experimentation such as routine screening."

Applicant also hereby submits a copy of Lee A. Phebus, et al., Life Sciences, Vol.61, No. 21, pp 2117-2126 (1997), attached hereto as **Exhibit B**, and a copy of Yao-Chang Xu et al., J. Med. Chem.,(2001), 44: 4031-4034, attached hereto as **Exhibit C**. Phebus et al. and Xu et al. provide evidence that the testing of 5-HT_{1F} compounds in binding assays to determine selectivity is routinely performed by those skilled in the art. Phebus et al. tested the binding of a 5-HT_{1F} receptor agonist at 56 other receptors. [See Lee A. Phebus et al (1997), page 2117, paragragh 1, lines 3-4; and Tables 1 and 2.] Xu et al. tested the binding of a 5-HT_{1F} receptor agonist at more than 40 other receptors. [See Yao-Chang Xu et al. (2001), page 4031, column 1, paragragh 1, lines 8-10; and Tables 2 and 3.]

Applicant maintains that new claim 25 which corresponds to previous claim 1, has been rewritten to clarify that the selective 5-HT_{1F} receptor agonist is not required to activate one of the other receptors recited. Rather, it does not activate <u>any</u> of the recited receptors to an extent within a factor of 10 of the extent to which it activates the 5-HT_{1F} receptor. More specifically, new claim 25 does not require that the 5-HT_{1F} receptor agonist binds to the recited receptors, but only that if it does bind, then the 5-HT_{1F} receptor agonist does not activate <u>any</u> of the recited receptors to the extent that it

activates the 5-HT_{1F} receptor. Hence, the term "selectively activates". Applicant maintains that one skilled in the art understands the meaning of "selectively activates". Moreover, claims 2, 7, 8, 13, 14, 19, and 20 have been similarly amended to further clarify the criteria for a selective 5-HT_{1F} receptor agonist.

In light of these amendments and remarks, applicant maintains that the Examiner's test #1 on page 4 of the November 18, 2002 Office Action is irrelevant when it states that "...any kind of 5-HT_{1F} receptor agonist which can activate the human 5-HT_{1F} receptor at least 10-fold more than it activates one of the receptors as recited in claims 1-24 can be used to treat human urinary incontinence". Applicant further points out that new claims 1-26 do not require that the 5-HT_{1F} receptor agonist activate <u>one</u> of the recited receptors, rather the invention requires that a <u>selective</u> human 5-HT_{1F} receptor agonist which will not activate any of the other recited receptor can be used to treat urinary incontinence.

Furthermore, Examiner's test #2 on page 4 of the November 18, 2002 Office Action is not relevant when it states "...any kind of 5-HT_{1F} receptor agonist can bind to the receptors as recited in claims 1-24". As stated hereinabove, applicant maintains that the claims do not require that the 5-HT_{1F} receptor agonist binds to the recited receptors, but only that if it does bind, then the 5-HT_{1F} receptor agonist does not activate any of the recited receptors to the extent that it activates the human 5-HT_{1F} receptor.

Applicant further maintains that given the present guidance in the specification, one skilled in the art can readily obtain and identify selective 5-HT_{1F} receptor agonists that can be used to

treat urinary incontinence.

Applicant maintains that no undue experimentation is necessary when considering the following eight factors: (1) the amount of experimentation is not excessive and is only routine for the skilled artisan; (2) the amount of guidance presented in the specification is sufficient; (3) working examples are presented; (4) the nature of the invention is a method to treat human urinary incontinence with 5-HT_{1F} selective agonists; (5) the state of the art provides that GPCR-selective compounds are useful in treating medical disorders; (6) the relative skill of those in the art is high; (7) the art is predictable given that the criteria for a selective compound is met and the GPCR mechanism is validated by predictive *in vivo* models; and (8) the breadth of the claims is reasonable given all of the above.

Applicant has further introduced new claim 26 which is dependent on claim 1. New claim 26 recites:

> The method of claim 1, wherein the 5-HT_{1F} agonist binds to the human 5-HT_{1F} receptor with a Ki value of 7.11 ± 0.76 nM or less.

Applicant maintains that the criteria recited in new claim 26 reflects the data in Table 1 on page 25 of the specification, wherein compound 1 binds to 5-HT_{1F} receptor with a binding affinity (Ki value) of 7.11 ± 0.76 nM and compound 2 binds to 5-HT_{1F} receptor with a binding affinity (Ki value) of 3.47 ± 0.08 nM. Applicant points out that the Examiner has acknowledged that claims for treating human urinary incontinence with compound 1 and compound 2 are enabled using the Ki values of these compounds is a reasonable way for applicant to define the invention.

Applicant maintains that claims 1-26 enable those skilled in the art to use the invention commensurate in scope with these claims

and no undue experimentation is required. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

In summary, in light of the remarks and amendments made hereinabove, applicant earnestly solicits allowance of the claims now pending in the subject application, namely, claims 1-26.

Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the following references which are on the attached Form PTO-1449 (**Exhibit D**). Accordingly, copies of the following references are attached to this Information Disclosure Statement:

1. U.S. Patent No. 5,360,735, Weinshank, et al., issued November 1, 1994, (**Exhibit 1**);

2. U.S. Patent No. 5,639,652, Weinshank, et al., issued June 17, 1997, (**Exhibit 2**);

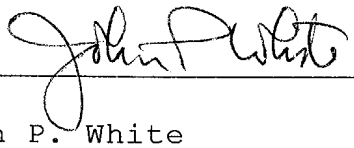
3. U.S. Patent No. 5,652,113, Weinshank, et al., issued July 29, 1997, (**Exhibit 3**); and

4. PCT International Publication No. WO 93/14201, Weinshank, et al., published July 22, 1993, (**Exhibit 4**).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided.

No fee, other than the enclosed fee of $446.00 ($410.00 for a two-month extension of time and $36.00 for additional filing fee), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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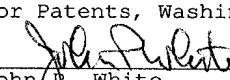
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



4/18/03

John P. White
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Date

Marked-up Version of the Amendments

Additions to the text are indicated by underlining; deletions are indicated by square brackets.

--1. (Three Times Amended) A method of treating urinary incontinence in a human subject suffering from urinary incontinence which comprises administering to [a] the human subject [suffering from urinary incontinence] a therapeutically effective amount of a 5-HT_{1F} receptor agonist which selectively activates the human 5-HT_{1F} receptor [at least ten-fold more than it activates each of the human 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_7 receptors].--

--2. (Amended) The method of claim 1, wherein the 5-HT_{1F} receptor agonist additionally activates the human 5-HT_{1F} receptor at least ten-fold more than it activates any [each] of the human 5-HT_{1B}, 5-HT_{1E}, 5-HT_{2B}, 5-HT_{5A}, 5-HT_{5B}, [and] or 5-HT_6 receptor[s].--

--7. (Amended) The method of claim 1, wherein the 5-HT_{1F} receptor agonist activates the human 5-HT_{1F} receptor at least 50-fold more than it activates any [each] of the human 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, [and] or 5-HT_7 receptor[s].--

--8. (Amended) The method of claim 7, wherein the 5-HT_{1F} receptor agonist additionally activates the human 5-HT_{1F} receptor at least 50-fold more than it activates any [each] of the human 5-HT_{1B}, 5-HT_{1E}, 5-HT_{2B}, 5-HT_{5A}, 5-HT_{5B}, [and] or 5-HT_6 receptor[s].--

--13. (Amended) The method of claim 7, wherein the 5-HT_{1F} receptor agonist activates the human 5-HT_{1F} receptor at least 100-fold more than it activates <u>any</u> [each] of the human 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, [and] <u>or</u> 5-HT_7 receptor[s].--

--14. (Amended) The method of claim 13, wherein the 5-HT_{1F} receptor agonist additionally activates the human 5-HT_{1F} receptor at least 100-fold more than it activates <u>any</u> [each] of the human 5-HT_{1B}, 5-HT_{1E}, 5-HT_{2B}, 5-HT_{5A}, 5-HT_{5B}, [and] <u>or</u> 5-HT_6 receptor[s].--

--19. (Amended) The method of claim 13, wherein the 5-HT_{1F} receptor agonist activates the human 5-HT_{1F} receptor at least 200-fold more than it activates <u>any</u> [each] of the human 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, [and] <u>or</u> 5-HT_7 receptor[s].--

--20. (Amended) The method of claim 19, wherein the 5-HT_{1F} receptor agonist additionally activates the human 5-HT_{1F} receptor at least 200-fold more than it activates <u>any</u> [each] of the human 5-HT_{1B}, 5-HT_{1E}, 5-HT_{2B}, 5-HT_{5A}, 5-HT_{5B}, [and] <u>or</u> 5-HT_6 receptor[s].--